IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

CUBIST PHARMACEUTICALS, INC.,	)	
Plaintiff,	)	
v.	)	Civil Action No. 12-367 (GMS) (CONSOLIDATED)
HOSPIRA, INC.,	)	
Defendant.	)	

DECLARATION OF BRUCE GANEM, PH. D.
IN SUPPORT OF HOSPIRA, INC.'S ANSWERING CLAIM CONSTRUCTION BRIEF

BRUCE GANEM, Ph.D., of full age, hereby declares as follows:

I. PERSONAL BACKGROUND

1. I am the same Bruce Ganem who submitted the *Declaration of Bruce Ganem, Ph.D. In Support Of Hospira, Inc.'s Opening Claim Construction Brief* on February 15, 2013 ("Ganem Decl. I").

2. I incorporate the Personal Background sections from the previous Ganem Declaration.

3. In developing my opinions set forth below, I have reviewed the Declaration Of William Gerwick, Ph.D. ("Gerwick Decl."). I have also considered the opening claim construction briefs submitted by Hospira, Inc. and Cubist Pharmaceuticals, Inc. A complete list of materials is included in Exhibit A attached hereto.

II. SCOPE OF OPINION

4. In this Declaration, I respond to the statements by Dr. Gerwick in the Gerwick Declaration regarding how the term "daptomycin" would have been used and understood by persons of ordinary skill in the art relating to U.S. Patent Nos. 8,058,238 and 8,129,342 (collectively, the "purity patents") as of their 2000 filing date.

III. A PERSON OF ORDINARY SKILL IN THE ART WOULD CONSIDER STEREOCHEMISTRY IMPORTANT TO UNDERSTANDING THE MEANING OF DAPTOMYCIN

5. It is a fundamental principle of chemistry, and one with which skilled scientists in the art as it relates to the purity patents would be familiar, that differences in stereochemistry between two enantiomers or diastereomers of a given drug can have profound chemical and biological consequences. Ganem Decl. I, ¶¶ 12-15. In the case of thalidomide, for example, the (*R*)-enantiomer of thalidomide has sedative attributes whereas the (*S*)-enantiomer of thalidomide is teratogenic and can cause severe birth defects. *Id.* at 12. Not surprisingly, "daptomycin" as its structure was incorrectly reported in the Baltz and Tally articles, and "daptomycin" as its corrected stereochemical structure is known today – the two being diastereomers – are also significantly different from each other. Daptomycin having the corrected structure with D-Asn is ten times more potent as an antibiotic than the daptomycin diastereomer having the structure with L-Asn as reported in the Baltz and Tally articles. JA507 Miao 2005 at 1520.[1]

6. Dr. Gerwick states that a person of ordinary skill in the art as it relates to the purity patents would not view corrections to the stereochemistry of a product "as a fundamental change," but rather as "a clarification to the characterization of the natural product." Gerwick

[1] Citations to the references cited herein will be made with respect to Exhibits ("Ex. __") that are attached hereto and submitted concurrently with this declaration, or to the Joint Appendix of Intrinsic Evidence ("JA ___").

Decl., ¶ 17. I strongly disagree with this statement. As I explained in my first declaration, "the daptomycin D-Asn diastereomer is a fundamentally different compound from the daptomycin L-Asn diastereomer." Ganem Decl. I, ¶ 33.

7. It is my opinion that a skilled scientist, when reading the purity patents as of their 2000 filing date, would consider the stereochemistry of daptomycin to be an essential factor in determining the meaning of the term "daptomycin." In particular, a person of ordinary skill in the art as it relates to the purity patents would recognize that because different diastereomers of a drug frequently have different physical and chemical properties, an understanding of the drug's stereochemistry is essential in determining how best to purify the drug. For example, different diastereomers typically have different physical properties such as HPLC retention times, as well as solubility and melting points, which can impact how they are purified. Thus, an appreciation and understanding of a drug's stereochemistry is an essential factor that informs the techniques used by a person of ordinary skill in the art in making and characterizing the drug.

8. Dr. Gerwick's own patents are consistent with my opinion that a skilled scientist would consider stereochemistry an important factor in characterizing a natural product. U.S. Pat. No. 8,034,780, for example, on which Dr. Gerwick is listed as an inventor, discloses and claims (as fully set forth in Formula (I) in columns 3 and 4) the natural product "Coibamide A," a peptide that is isolated from a marine cyanobacterium. Ex. B, '780 patent at col. 3, l. 65 - col. 4, l. 6 The patent goes to great lengths in trying to elucidate the structure of the natural product using spectroscopic techniques. The patent also discloses and claims enantiomers and diastereomers of the natural product. *Id.* at col. 4, ll. 6-17; col. 8, ll. 62-67; claim 1. Of particular interest, Dr. Gerwick systematically attempts to elucidate the detailed stereochemical configuration of Coibamide A. *Id.* at Col. 17, ll. 1-40. In part, because the component amino

acid residues of Coibamide A can occur in either the L- or D-configurations, the '780 patent states:

> The peptidic molecular structure of coibamide A presents a large number of possible combinations and permutations of component amino acid residues for structure activity relationship studies and/or drug development (e.g., increase bioavailability and/or decrease toxicity).

Id. at col. 19, lines 45-52. Thus, in his own work with isolating natural peptides from nature, Dr. Gerwick recognized the importance of stereochemistry – its potential for significant impact on Coibamide A in terms of its applicability as a drug.

9. Thus, contrary to Dr. Gerwick's statements in his declaration, it is my opinion that a person of ordinary skill in the art, when reading the purity patents, would consider the specific stereochemistry of daptomycin particularly important. As explained above, daptomycin L-Asn and daptomycin D-Asn are "fundamentally different compound[s]" and Miao's 2005 "unexpected" discovery of daptomycin's stereochemistry led to "a completely new understanding of the structure of daptomycin." Ganem Decl. I, ¶ 33.

I declare under penalty of perjury under the laws of the United States that the foregoing is true and correct.

Executed this 8th day of March, 2013.

Bruce Ganem, Ph.D.